

Amendments to the Claims:

1. (Previously Presented) A transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin wherein a part or a whole of TRIF-related adaptor molecule (TRAM) genes on its chromosome is deleted, a function of expressing TRAM which is expressed in a wild-type is lacked, and responsiveness to a ligand recognized by TLR4 is specifically impaired.

2. (Previously Presented) The transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin according to claim 1, which is responsive to PGN, R-848 and CpG ODN, and non-responsive to LPS.

3. (Canceled)

4. (Currently Amended) A method for screening a substance promoting ~~or~~ suppressing a response to a ligand recognized by TLR4, wherein a test substance is administered to an immunocyte derived from the knock out mouse of claim 1 or 2 and to an immunocyte derived from a wild-type mouse, and wherein the following responses (a) to (c) to the ligand recognized by TLR4 are measured in a immunocyte derived from the transgenic homozygous TRAM knock out mouse non-responsive to endotoxin according to claim 1 or 2 is measured/estimated, with the use of the immunocyte, a test substance and the ligand recognized by TLR4:

- (a) cytokine (TNF α , IL-6 and IL-12p40) production of macrophage;
- (b) splenocyte proliferation, and up-regulation of surface molecules; and
- (c) expression of signaling molecules inducing IFN- β production;

wherein a response for one or more of (a), (b), or (c) in the immunocyte derived from said wild-type mouse but not in the immunocyte derived from said knock out mouse indicates that the test substance promotes a response to a ligand recognized by TLR4.

5. (Currently Amended) A method for screening a substance promoting ~~or~~ suppressing a response to a ligand recognized by TLR4, wherein a test substance is administered

to the knock out mouse of claim 1 or 2 and to a wild-type mouse, and wherein the following responses (a) to (c) to the ligand recognized by TLR4 are measured, with the use of the transgenic homozygous TRAM knock out mouse, a test substance and the ligand recognized by TLR4:

- (a) cytokine (TNF α , IL-6 and IL-12p40) production of macrophage;
- (b) splenocyte proliferation, and up-regulation of surface molecules; and
- (c) expression of signaling molecules inducing IFN- β production;

wherein a response for one or more of (a), (b), or (c) in said wild-type mouse but not in said knock out mouse indicates that the test substance promotes a response to a ligand recognized by TLR4.

6-7. (Canceled)

8. (Previously Presented) An immunocyte from the transgenic homozygous TRAM-knock out mouse non-responsive to endotoxin according to claim 1 or 2.